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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/913,918	12/08/1997	DARWIN J. PROCKOP	TJU-1857	7733

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	PAPER NUMBER
1632	37

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/913,918	PROCKOP ET AL.	
	Examin r	Art Unit	
	Dave Nguyen	1632	

-- The MAILING DATE of this communication app ars on the cover sh t with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-71 and 76-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-71 and 76-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

Claims 72-75 have been canceled by the amendment filed Feb. 26, 2002.

Claims 69-71, 76-112 are pending.

Elected claims 69-71, 77, and 97-112 readable on the species of osteoporosis and obesity factor, to which following grounds of rejection are applicable, are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:.

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 109-111 remain rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

A method of providing a protein to a mammal, the method comprising implanting within the mammal a container containing an isolated marrow stromal cell which comprises an expressible gene construct encoding the protein,

wherein the container physically isolates the stromal cell from immune cells of the animal, and

wherein the container has pores which permit diffusion of the protein between the interior and exterior of the container.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims readable on embodiment within the context of *ex vivo* gene therapy of using any genetically modified stromal cells expressing a therapeutic DNA to treat any animal afflicted with a disease, disorder, or condition characterized by a defect in said DNA in the animal.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance

presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The application indicates that implantation of mesenchymal cells from normal mice into irradiated transgenic mice that expresses the mutated COL1 A1 gene led to production of progeny cells that express the normal proα(1) chains in the irradiated mice. The application further contemplates that long-term expression of any therapeutic protein encoded DNA including the obesity gene (Ob) can be achieved for therapeutic application of the gene in the treatments of obesity or decrease of appetite in any animal by using any autologous or non-autologous stromal cell (not necessarily limited to mesenchymal cells (MSC)) having any Ob expressing DNA vector incorporated therein.

While the application including the state of the prior art provides sufficient guidance and reasonable enablement for an improved methods of using claimed container to express a recombinant protein for non-therapeutic applications that are well known to a skilled artisan at the time the invention was made, the application on the basis of applicant's disclosure does not provide any reasonable enablement including sufficient guidance and/or factual evidence so as to reasonably extrapolate from a simple production of endogenous COL1 A1 proteins by allogeneic MSC in transgenic mice expressing the mutated COL1 A1 protein to any therapeutically relevant effect in any animal having a real-world medical disease associated with a protein defect, particularly given that *ex vivo* gene therapy of using bone marrow stromal, stromal stem cells or mesenchymal stem cells is an emerging technology that remains reasonably unpredictable at the time the invention was made (see Marshall (Science, Vol. 269, pp. 1050, 1995), Verma *et al.* (Nature, Vol. 389, pp. 239-242), Anderson (Nature, Vol. 292, 25-30, 1998), Moritz *et al.* (J. Clin. Invest. 1994, 93:1451-1457), Riddell *et al.* (Nature Medicine, Vol. 2, 2:216-223, 1996), Onodera *et al.,* Acta Haematologica, 101, 2, pp. 89-96, 1999, Kohn , Current Opinion in Pedatrics, 7, 56-63, 1995).

The specification does not provide reasonable enablement for claims encompassing *ex vivo* gene therapy methods as claimed, wherein any administration route is employed, wherein any genetically

modified stromal stem cell is employed, and wherein any disease as disclosed in the claims is contemplated.

More specifically as to the state of the art of *ex vivo* gene therapy of using bone marrow stromal cells including stromal stem cells, the state of the art exemplified by Marshall (Science, Vol. 269, pp. 1050, 1995) indicates that in 1995, "so far, there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" and that "while there are several reports of convincing gene transfer and expression, there is still little or no evidence of therapeutic benefit in patient or even in animal models" (page 1050). More specifically as the unpredictability of using retroviral vectors which has been preferably used in experimental protocols *in vitro* and/or *in vivo,* due to its ability to better express a recombinant protein in stem cells as compared to other viral or non-viral vectors, Verma *et al.* (Nature, Vol. 389, pp. 239-242) teach that "another formidable challenge to the *ex vivo* approach is the efficiency of transplantation of the infected cells" and that "successful animal models will prove inadequate when the same protocols are extended to humans" (page 240, column 3, last paragraph). The specification, for example, contemplates that by employing any retroviral trasnduced MSC as carrier of protein drugs in any *ex vivo* gene therapy method, the stem cells would function as a continuous supply of protein drugs to any target site *in vivo,* such that any disease or disorder can be treated therapeutically in any animal. A skilled artisan, attempting to make and use the claimed constructs, would first look to the specification for guidance as to which therapeutic protein drug encoded DNA to use in an *ex vivo* gene therapy wherein retroviral transduced bone marrow stromal or stromal stem cells are employed for treating a disorder. However, the state of the prior art of record indicates that there are many problems to be overcome before all vector systems including retroviral vectors effect a contribution to medicine. Next, the artisan would look to the specification for guidance as to which compositions among the disclosed compositions, *e.g.,* genetically modified cells expressing any protein, receptor, or enzyme for use in for the intended purpose of achieving a therapeutic effect as the result of protein drug expression, the specification provides little guidance for one skilled in the art to determine, without undue experimentation, as to which of the genetically modified stromal stem cell exhibit the intended "protein drug" effect in any animal having a

disease, disorder, or condition as contemplated by the as-field specification.

More specifically with respect to claims directed enzyme therapy in the context of *ex vivo* gene therapy, even after 10 years from the effective filing date, Anderson (Nature, Vol. 292, 25-30, 1998) with respect to an experiment study on human ADA patients wherein autologous T cells are employed as carriers of ADA transduced retroviral vectors states that "although both girls have gene-engineered T lymphocytes in their circulation after more than 7 years, no definitive conclusion after more than 7 years, no definitive conclusion can be drawn as to the relative roles of PEG-ADA and gene therapy in their excellent clinical course". The fact that no working examples have been shown by the as-filed specification to conclusively show a therapeutically relevant effect in an animal having a real world medical condition associated with a protein defect, coupled with the unpredictability of gene therapy as expressed by the art of record, does not provide sufficient evidence for a skilled artisan to reasonably extrapolate, without any undue experimentation, from the basis of applicant's disclosure to any therapeutically useful effect by using any protein encoded vector contained in any bone marrow stromal cell encapsulated by any container as contemplated by the claimed invention.

While the as-filed specification indicates that by using a container known in the prior art, *e.g.,* diffusion chambers, polymeric capsule, the genetically modified bone marrow stromal cells will be insulated or physically isolated from an immune response, thereby contemplating that a therapeutically relevant effect can be generated by the cells due to the protection of the administered stromal stem cells by any container from the immune response of the treated animal. However, in addition to *in vivo* transient gene expression by an expression vector and the destruction of the diffused stromal stem cells by the immune response before the cells produce a sufficient amount of protein at a desire target site to produce a therapeutically relevant effect, Riddell *et al.* (Nature Medicine, Vol. 2, 2:216-223, 1996) reaffirmed the unpredictability of *ex vivo* gene therapy methods wherein foreign cells and/or proteins are employed at the time th invention was made by indicating that even with the use of autologous cells expressing a foreign protein, HIV-infected patients when grafted with autologous cytotoxic CD8+ T cells induce strong primary T-cell immune responses to foreign antigens expressed by transferred autologous

cytotoxic CD8+ T cells (p. 221, column 1), and that the rejection of genetically modified cells and/or foreign proteins by even immunocompromised hosts suggests that *ex vivo* gene therapy by using foreign protein expressed transiently by even autologous cells is not routine or conventional in the prior art at the time the invention was made.

In addition, it is not clear how the systemic administration of genetically modified bone marrow cells which harbor a foreign receptor on the cell surface, for example, would not be destroyed by the immune response that is mounted against the foreign receptor expressed on the surface of the genetically modified cells after their diffusion from the container. Even if some of the genetically modified stromal stem cells and/or recombinant proteins escape from the immune response in a survived host after an administration or implantation, it is further not apparent how the genetically modified stromal stem cells traverse though barriers such as peripheral vein and endothelial wall to reach a disease site so as to generate a therapeutically relevant effect. Note also that Hoeben *et al.* (Human Gene Therapy, 4, 179-186, 1993) provides factual evidence showing that even if the genetically modified implanted fibroblast cells expressing a therapeutic protein, *e.g.,* factor VIII, survive the immune response of a recipient mouse which is immuno-deficient, there is no evidence of any recombinant Factor VIII in the plasma samples of recipient mice (abstract). The absence and/or *in vivo* transient expression of a recombinant protein in even a small animal such as immuno-deficient mice, and a rapid clearing of the introduced recombinant protein from mouse's serum as shown in the prior art of record, does not lend any credible evidence to support applicant's claim that any stromal stem cell when carrying a protein drug encoded vector can be employed as a stable bioreactor to provide a continuous supply of protein drugs in any animal having any disease or disorder, such that a therapeutically relevant effect can be generated. Thus, where *ex vivo* gene therapy using any coding sequence of any protein is not reasonably predictable in establishing a therapeutic outcome of gene therapy for all types diseases, the gene therapy methods referred to in the present claims are also not predictable, nor is it apparent as to how a simple expression of endogenous protein from non-genetically modified MSC in transgenic mice as exemplified in the specification is reasonably correlated to a therapeutic effect in any animal having any disease as claimed.

Furthermore, the state of the art exemplified by Moritz *et al.* indicates that *ex vivo* gene therapy using genetically modified cell for engraftment into any an animals remain unpredictable. More specifically, the Moritz *et al.* reference (J. Clin. Invest. 1994, 93:1451-1457) indicating that "although gene transfer and long term gene expression in repopulating stem cells have been achieved in murine models by a number of investigators, *in vivo* experiments in larger animals such as dogs and primates have met with limited success, largely because of the low efficiency of infection of primitive hematopoietic stem cells"

The art of record clearly indicates that the efficiency of gene transfer into stem cells was much lower when similar protocols were assessed in large mammals and in human gene therapy trials, suggesting that there are species-specific differences in the susceptibility of stem cells to retrovirus infection. There are no working examples in the specification which indicates the efficiency of vector transduction in any stromal stem cell of any mammal including humans wherein a therapeutic effect is generated. Thus, in absence of any *in vivo* data regarding the grafting methods in any and/or all animals other than a murine model, it is not apparent how one skilled in the art determines the appropriate combination of transfection method, level of expression, cell numbers and method of administration for each possible gene, so as to have a therapeutic effect in any and/or all animals, without undue experimentation.

More specifically as to the state of the art of *ex vivo* gene therapy of employing any genetically modified hematopoietic cell expressing a transgene coding for an Ob protein, Onodera *et al.,* Acta Haematologica, 101, 2, pp. 89-96, 1999, indicates that even in 1999, the retroviral-mediated gene transfer to hematopoietic stems was insufficient for achievement of any therapeutically relevant effect (abstract). Kohn , Current Opinion in Pedatrics, 7, 56-63, 1995, indicates that the efficiency of gene transfer into stem cells was much lower when similar protocols were assessed in large mammals and in human gene therapy trials, suggesting that there ar species-specific differences in the susceptibility of stem cells to retrovirus infection" (p. 58, column 1). Kohn further teaches that effective gene therapy for hematologic disorders remains unpredictable, and that a detection of circulating vector sequences in the blood *in vivo*

after a transplantation of hematopoietic stem cells containing gene therapy vectors is not equivalent to a therapeutic effect (page 59, columns 1 and 2). There are no working examples in the specification which indicates the efficiency of transduction in bone marrow stromal or stromal stem cells of any mammal including humans wherein a therapeutic effect is generated.

Thus, it is clear from the evidence of record that that *ex vivo* gene therapy as claimed is not reasonably predictive and not yet shown to be successful. Applicants have not provided any convincing evidence that their claimed invention is indeed useful as a therapeutic for the treatment of any disease, disorder or condition as listed or contemplated by the as-filed specification, and have not provided sufficient guidance to allow one skilled in the practiced the claimed invention without undue experimentation for the contemplated breadth of the claims. In absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

In view of the lack of guidance regarding the administration parameters, lack of working examples, breadth of the claims, state of the art and the unpredictability of the art, as set forth by the evidence presented above, undue experimentation would be required by one of ordinary skill to practice the invention in the context of therapeutic application of *ex vivo* gene therapy as claimed.

Applicant's response (pages 3-5) has been considered by the examiner but is not found persuasive for the reasons of record and in view of the following reasons:

Applicant asserted on page 3 that Applicant need not have actually reduced the invention to practice prior to filing, that there is no undue experimentation to practice the invention, that the *ex vivo* gene therapy for correction of any disease or defect is conventional and routine at the time of filing, that as evidenced by Verma, the level of a skilled artisan is high, and that Verma demonstrates that gene therapy can and does work, *e.g.,* also citing MPEP 2164.01, *In re Angstadt, In re Buchner, In re Robins,* MPEP 2164.02, *Gould v Quigg,* applicant's comments are not found persuasive because on the contrary to applicant's assertion, the state of art of *ex vivo* gene therapy for the intended purpose of correction of any disease or defect in any mammal including humans remains unpredictable even years after the effective filing date of the application.

Moreover, whether a DNA construct has been developed and shown to be expressed *in vivo* after

an implantation of a carrier such as genetically modified cells, diffusion chambers containing the carriers, is not the same as claiming that any *ex vivo* gene therapy of using any protein encoding DNA in applicant's stroma cells and containers having pores is routine, not undue and conventional. The issue is that the scientific community is having a difficulty in developing generally an *ex vivo* gene therapy method that can be generally employed for use to treat any disease or defect in a real-world mammal such as domestic large mammals and humans. Applicants do not explain with clear and convincing evidence as to why the assessment of the field by skilled artisans of record is wrong as it applies to the broadly claimed subject matter for therapeutic applications in any mammal having any disease or defect. Based on the findings above-that all of the Wands factors other than the level of skill in the art weigh in favor of nonenablement: It is the examiner's position that the specification does not provide adequate guidance to enable practice of the claimed invention without undue experimentation. Rather, as in a recent Federal Circuit case, the "teachings set forth in the specification provide no more than a 'plan' or 'invitation' for those of skill in the art to experiment practicing any *ex vivo* gene therapy method in any mammal having any disease or defect so as to further study the physiological activity of the exogenous protein being expressed by the implanted stroma cells to plan for future work on the making of a putative *ex vivo* gene therapy method that would overcome the obstacles that were expressed in the art of record...; they do no provide sufficient guidance or specificity as to how to execute that plan." In re Wright, (CA FC) 27 USPQ2d 1510 (1993), Enzo Biochem Inc. v. Calgene Inc., 188F .3d 1362, 1374, 52 USPW2d 1129, 1138 (Fed. Cir. 1999). See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

Applicant asserted on page 4 that applicant have provided evidence of therapeutic benefit in an animal model, however, applicant's assertion is not persuasive because it appears that applicant refers to the transgenic murine model having COL1 A1 being expressed in the germline. Such transgenic model whereby a completely distinct technique was used to create such model

is not the same as claiming an *ex vivo* gene therapy method that contemplates an implantation of carriers containing stromal cells expressing a therapeutic protein in a non-transgenic but diseased or defect bearing mammal. Even if some gene therapy methods disclosing particular techniques and genes have been shown to work after the filing date of the invention, such methods are not only reasonably extrapolated to the state of the art of *ex vivo* gene therapy at the time of filing but also cannot be used to support applicant's enablement of the broadly claimed subject matter at the time the invention was made. Applicant further assert that the unpredictability of HSC *ex vivo* gene therapy is not relevant to the claimed invention, however, such assertion is not found persuasive because just like HSC, stromal cells are used as carriers to express a therapeutic protein to treat any disease or disorder in any mammal. Just like problems encountered in other *ex vivo* gene therapy methods of employing progenitor cells to express a therapeutic protein, by simply using a different carrier such as stromal cells would not solve problems encountered in *ex vivo* gene therapy methods such as the transient gene expression by the vectors being used to transfect stromal cells, the transient level of the expressed exogenous proteins due to exposure to the immune response, the targeted problem of the already depleted level of the exogenous proteins floating in the treated mammal. Applicants have not shown any evidentiary support to demonstrate that stromal cells by being just cell carrier are any different that other cell carriers so as to reasonably convey to a skilled artisan at the time of filing that *ex vivo* implantation of genetically modified cells can be used as a magic or master bullet to treat any disease or disorder in any mammal at the time the invention was made. Even if assuming for argument, Applicant were able to show a particular therapeutic effect generated from the use of a particular gene encoding a therapeutic protein in an art recognized animal model, such showing is not commensurate to the broadly claimed subject matter as a master method to treat any disease or defect in any mammal. The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of

> ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 488, 496 & n.23. 30 USPQ2d 1438, 1445 & n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation for those skill in the art to experiment with applicant's DNA *ex vivo* gene therapy of employing genetically modified stromal cells for producing any therapeutic effect as intended by applicants at the time the invention was made. At best, the claimed invention as claimed in claim 112 is enabled as an improved tool of carriers to be used in a simple method of expressing an exogenous protein in a mammal.

The following prior art is cited so as to further substantiate the examiner's position, which is that the state of the art of *ex vivo* gene therapy at the time of filing (1995) remains unpredicatable.

Orkin *et al.,* 1995, the NIH report.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 69-71, 99-108 and 112 are rejected under 35 USC 102(e) as being unpatentable over Greenberger *et al.* (US Pat No. 5,962,323) or Emerson *et al.* (US Pat No. 5,670,351), each of which taken

with any of Caplan *et al.* (US Pat No. 5,197,985), Schinstin *et al.* (US Pat No. 5,843,431), Mardon (previous cited prior art), and as evidenced by applicant's admission of the prior art of record as indicated on page 6 bridging page 7, and page 27 of the specification.

Greenberger *et al.* and Emerson *et al.* both teach a method of using cultured bone marrow stromal cells for implantation and providing a protein of interest to a cell in a mammal for research in animal models such as canine models, wherein the cells are genetically modified cells to express a recombinant protein of interest (entire documents, Greenberger *et al.* and Emerson *et al.*. and also the teaching of implantation of isolated-genetically modified mesenchymal stem cells in Greenberger *et al,* columns 7-10, Emerson *et al.,* columns 7-8, claim 2 on column 49). In addition, vectors containing regulatory sequence operably linked to a transgene of interest including a marker is routine and conventional in the art for cell trasnfection and would have been obvious as minor modifications, as evidenced on columns 8-9 of Greenberger *et al.* Greenberger *et al.* and Emerson *et al.* do not teach the use of a microcarrier, diffusion chamber, or microcapsule to control and/or enhance the delivery and release of the isolated bone marrow stromal cells.

However, at the time the invention was made, the prior art of record, as exemplified by Caplan, Schinstin *et al.,* and Mardon, does teach that it is routine and conventional to use a microcarrier, diffusion chamber, or microcapsule to enhance the delivery and subsequent release and differentiation of the implantable mesenchymal stem cells to the target site (see entire document of each of the cited reference). Furthermore, the specification teaches on page 3 bridging page 7 that immunological isolation means include well known technologies and devices such as microencapsulation, diffusion chambers, etc.

It would have been obvious for one of ordinary skill in the art to have employed any known a microcarrier, diffusion chamber, or microcapsule to enhance the delivery and subsequent release of the implantable mesenchymal stem cells disclosed in Greenberger *et al.* and Emerson *et al.* to the target site. One of ordinary skill in the art would have been motivated to have employed a microcarrier, diffusion chamber, or microcapsule to enhance the delivery and subsequent release of the implantable mesenchymal stem cells to the target site because of the reasons set forth in the immediately preceding

paragraph. Note that use of well known technologies and devices such as microencapsulation, diffusion chambers, etc., as taught by the combined cited references, would physically isolate the isolated genetically modified stromal cells from the immune response, as evidenced by applicant's admission of the prior art of record as indicated on page 6 bridging page 7 of the specification.

In addition, one of ordinary skill in the art would have been motivated to transfect or transduce the cells of Greenberger *et al.* and Emerson *et al.* by conventional methods with vectors containing any known promoter, signal sequences, beneficial protein, and/or a coding sequence of a selectable marker, such as those disclosed in the cited references to determine and track the effect of these regulatory elements and the subsequent expression of a desired gene during the differentiation of the stromal cells once implanted in an animal model, as disclosed in Greenberger *et al.* and Emerson *et al.*. references.

It would also have been obvious for one of ordinary skill in the art to have employed any pore size in any of the containers available in the prior art of record as an obvious matter of design choice particularly since such modifications would be expected to lead to an equivalent enhancement in delivery, release, expression and differentiation of the cells at the target delivery site, particularly in view of the absence of factual evidence showing an unexpected property of the use of the claimed pore size relative to those outside the claimed diameter of the pores of the claimed containers.

Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 69 and 77 are rejected under 35 USC 102(e) as being unpatentable over Greenberger *et al.* or Emerson *et al.* each of which taken with any of Caplan *et al.* (US Pat No. 5,197,985), Schinstin *et al.* (US Pat No. 5,843,431), Mardon (previous cited prior art), and as evidenced by applicant's admission of the prior art of record as indicated on page 6 bridging page 7 of the specification, and further in view of Beresford *et al.* and Flier (cited in the previous office actions).

The rejection of the base claim 69 as being unpatentable over Greenberger *et al.* and Emerson *et al.*, each of which taken with any of Caplan *et al.*, Schinstin *et al.*, Mardon (previous cited prior art), and as

evidenced by applicant's admission of the prior art of record, is applied here as indicated above.

The combined cited references do not teach that the recombinant protein encoded DNA is the obesity factor encoded DNA.

However, at the time the invention was made, Beresford *et al.* disclose that rat marrow stromal cell cultures are capable of defferentiating into adipocytic and osteogenic cells, and further, are capable of expressing collagens (type I, III, and IV). The relative amounts of cells which differentiate into adipocytes and osteogenic cells, as well as the relative types and amounts of collagens synthesized by the cells is dependent of the culture conditions of the stromal cells (see page 344-345, under "Collagen synthesis", and page 348, left column, second paragraph). As the obesity factor encoded DNA is expressed in adipocytes (see Flier), one of ordinary skill in the art would have been motivated to generate a vector construct containing the obesity factor encoded DNA, operatively linked to regulatory elements associated with collagens types I, III and IV for the purpose of determining the effect of these regulatory elements on the expression of the obesity gene, and the effect of the obesity gene in stromal cells during differentiation into adipocytes or osteogenic cells. Moreover, as the references disclose transfecting stromal cells with expression vector constructs comprising a gene of interest, and in view of the teachings of Flier that the obesity protein is expressed in cells of the mesenchymal cells (stromal cells) lineage, one of ordinary skill in the art would have had a high expectation of successfully transfecting stromal cells with an expression vector encoding an obesity factor, such that the transfected cells synthesize the obesity factor, which has previously been established to occur in differentiated cells of the stromal cell lineage, barring evidence to the contrary.

Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's response (pages 5-8) has been considered by the examiner but is moot in view of the new grounds of rejection as set forth above.

No claims are allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER